compound is not administered.

19. (new) The method of claim 1, wherein said first compound is selected from the group consisting of butyrate, phenylbutyrate, 4-phenylbutyrate, and a biologically active analog of butyrate or phenyl butyrate and said second compound is selected from the group consisting of isoflavone and a flavone.

REMARKS

The March 12, 2003 Official Action and references cited therein have been carefully reviewed. In light of the amendments presented herewith and the following remarks, favorable reconsideration and allowance of the application are respectfully requested.

At the outset, claims 5 and 13 have been amended to correct a typographical error. Support for these amendments can be found at page 19, lines 6-11 and 25-27, and page 20, lines 5-8, as well as in the original claims. New claim 19 has been added support for this claim can be found in original claims 4 and 5.

The Examiner has made a rejection under 35 U.S.C. §112 first paragraph, asserting that the specification allegedly fails to enable the full scope of the claims. It is the Examiner's position that the compounds of the claims are defined solely by functional limitations, and therefore it would require undue experimentation to identify the compounds which meet the specified limitations.

The Examiner has also rejected claims 1-18 under 35 U.S.C. §103(a) as allegedly unpatentable over US Patents 5,972,995, and 6,329,422, both to Fischer et al. It is the Examiner's position that Fischer et al. teach a method of enhancing chloride transportation in epithelial cells by contacting the cells with a flavone or an isoflavone. The Examiner states that Fischer et al. also teach a method of

treating cystic fibrosis, including administration of such agents orally, or by an inhaler. In connection with this §103 rejection, the Examiner also asserts that while these references do not explicitly teach the rejected methods of administration, or instantly claimed kits, these aspects of the invention are allegedly obvious.

The foregoing constitutes the entirety of the objections and rejections raised in the March 12, 2003 Official Action. In light of the present claim amendments and the following remarks, each of the above-noted rejections under 35 U.S.C. §§ 112, first paragraph, and 103 is respectfully traversed.

THE CLAIMS ARE FULLY ENABLED BY THE DISCLOSURE IN THE SPECIFICATION

The Examiner states that "Claims" are rejected under 35 U.S.C. §112, first paragraph, asserting that the specification allegedly fails to provide enablement commensurate in scope with the present claims. Because the Examiner has not specified which claims are rejected, Applicants have addressed the rejection as though it pertains to all pending claims.

The Examiner asserts that because the recited compounds are defined by function only, the specification does not enable the full scope of claims.

Applicants respectfully submit, however, that the full scope of the claims is enabled by the present specification. As noted in the MPEP at § 2164,

> The information contained in the disclosure of an application must be sufficient to inform those skilled in the relevant art how to both make and use the claimed invention. Detailed procedures for making and using the invention may not be necessary if the description of the invention itself is sufficient to permit those skilled in the art to make and use the invention. [*Emphasis supplied.*]

> In § 2164.01, the MPEP continues,
> The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

(*Quoting United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988).

The Examiner's rejection states that the instant claims rely on functional language as the point of novelty (Official Action page 3, second paragraph.) The Examiner cites *General Electric Company v. Wabash Appliance*, and *University of California v. Eli Lilly Co.* as evidence that claims which use functional language as the point of novelty are not enabled.

However, contrary to the Examiner's assertion, the instant claims do not use functional language as the point of novelty. The compounds described in functional terms in the instant claims (ie. compounds which enhance the trafficking of a mutant CFTR polypeptide to the surface of an epithelial cell, or increase the chloride ion transport activity of a mutant CFTR polypeptide at the surface of an epithelial cell) are not the point of novelty of the invention. Rather, the point of novelty, is the chronic intermittent treatment schedule by which the compounds are administered (see pages 8-9 of the specification.) All of the claims explicitly recite this feature. Accordingly, the arguments and case law set forth by the Examiner are inapplicable to the instant claims.

Further, applicants submit that in the instant case, the functional language is used to describe phenomena which are well known in the art. Additionally, Applicants provide explicit examples of compounds which satisfy the functional language of the claims. It is therefor clear that identification of a compound which meets the limitations set forth in the claims would comprise routine experimentation for

the skilled artisan. This is because it is well established that cystic fibrosis is often characterized by decreased trafficking of a CFTR polypeptide and/or a deceased chloride ion transport. Evidence of this is provided throughout the instant specification, for example at page 3, line 36-page 4, line 9, page 16, line 9-page 17, line 23, and page 23, lines 9-27. Further, there are numerous compounds which are known to be useful for improving CFTR polypeptide trafficking to the cell surface, or for improving chloride ion transport at the cell surface. These compounds are described throughout the specification, for example at page 19, line 12-page 20, line 8, and in the examples. Finally, it would be relatively easy to test how a particular compound affected CFTR polypeptide trafficking to the cell surface, or chloride ion transport at the cell surface. Various screening methods which could be utilized are detailed throughout the specification, for example at page 22, lines 12-31. Thus a skilled artisan could readily determine via routine experimentation what compounds meet the functional limitations of these claims.

Applicants also note that the patents relied on by the Examiner in support of the rejection of claims 1-18 under §103 include disclosure relating to compounds which enhance chloride transport or protein trafficking. For example, at column 8, lines 10-29, US Patent 6,329,422 describes numerous flavones and isoflavones, for enhancing chloride transport, and various assays for testing this effect. Therefore, the meaning of the functional language in the instant claims is well established in the art. Further, it is a well-settled premise in patent law "that the specification need not teach and preferably omits that which is well-known to those skilled in the art. In re Buchner, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987); and Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co., 730 F.2d

1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984). Therefore, in light of the preponderance of evidence that compounds which meet the functional limitations of the claims are well known in the art and methods for screening such compounds are routine, applicants submit that the requirements for enablement have been met. Accordingly, one must conclude that the disclosure does provide sufficient information for practice of the invention with regard to compounds which enhance the trafficking of a mutant CFTR polypeptide to the surface of an epithelial cell, or increase the chloride ion transport activity of a mutant CFTR polypeptide at the surface of an epithelial cell.

Therefore, Applicants respectfully submit that the claims as amended fully comply with all the requirements of 35 U.S.C. §112, first and second paragraph and request that the rejection of the claims under 35 U.S.C. §112, first and second paragraph be withdrawn.

CLAIMS 1-18 AS AMENDED ARE PATENTABLE OVER US PATENTS 5,972,995 AND 6,329,422 TO FISCHER ET AL.

The Examiner has rejected Claims 1-18 under 35 U.S.C. §103 (a) as allegedly unpatentable over US Patents 5,792,995 and 6,329,422 to Fischer et al.

The relevant inquiry in determining obviousness under 35 U.S.C. §103 based on the combined disclosure of references, is whether the references supply some teaching or suggestion to one of ordinary skill in the art to arrive at the invention as claimed. In re Dow Chemical Company, 5 U.S.P.Q.2d 1529 (Fed. Cir. 1988). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion supporting the combination. In re Fine, 5 U.S.P.Q.2d 1596 (Fed. Cir. 1988). Moreover, the teaching or suggestion supporting the desirability or the combination must be found in the prior

art, not in the applicant's disclosure. In re Fritch, 23 U.S.P.Q.2d 1780 (Fed. Cir. 1992). Under these standards, neither of the cited references, considered singly or in combination, renders obvious the claimed invention.

It is the Examiner's position that the Fischer patents teach a method of enhancing chloride transportation in epithelial cells comprising contacting the cell with a flavone or isoflavone. The Examiner acknowledges that the Fischer patents do not teach the chronic intermittent treatment schedule of the instant invention. However, the Examiner contends that adjusting the timing of administering two active agents would be obvious, because optimization of a result effective variable is considered within the skill of the artisan.

Applicants agree that the Fischer et al. patents do not teach or suggest the specialized, novel chronic intermittent treatment protocol which is critical to the practice of the instant invention. However, applicants do not agree that this treatment schedule is obvious over the teachings of the Fischer patents.

The chronic intermittent schedule of the invention is disclosed at pages 8-9 of the specification, and is quite different from routine treatment protocols, such as those disclosed in the Fischer et al. patents. For example, the chronic intermittent schedule of the invention includes one to two weeks of administration, followed by a two to four week period in which the patient is not treated. Further, the chronic intermitted treatment protocol includes concurrent and staggered administration of the drugs of the invention. Such a treatment schedule prevents the undesirable induction of tolerance to the compounds, thereby providing an improved protocol for the beneficial treatment of cystic fibrosis.

Neither of the Fischer patents provides any significant guidance regarding a specific or particular administration

protocol. Instead, an extremely broad dosage range (2-30 g/daily) is given. Further, there is no mention or suggestion in the Fischer et al. patents to discontinue administration for periods of time, as is critical to the instantly claimed chronic treatment protocol. It is a well-settled premise in patent law that "silence in a reference is not a proper substitute for adequate disclosure of facts from which a conclusion of obviousness may justifiably follow". In re Burt, 148 U.S.P.Q. 548 (CCPA 1966).

In fact, careful examination of the teachings of the Fischer et al. patents reveals that the chronic administration schedule instantly claimed would be counterintuitive, according to the teachings of the Fischer patents. Specifically, the Fischer et al. patents explicitly describe their dosage protocol at column 7, lines 44-64 of 5,972,995 and column 13, lines 37-57 of 6,329,422. In both cases, all of the dosage protocols require daily administration. Accordingly, the skilled artisan would reasonably conclude from the Fischer et al. patents that the periods without drug administration, which are part of the instantly claimed chronic intermittent administration schedule, would inhibit treatment efficacy. Therefor applicants submit that the Fischer et al. patents teach away from the instant treatment protocols, because the Fischer patents require daily administration of the recited compounds. Consequently, the instant methods, which include a chronic intermittent administration schedule, are not obvious over Fischer et al.

Next, it is respectfully submitted that the chronic intermittent schedule disclosed in the instant application produces an unexpectedly enhanced therapeutic effect, which is evidence of non-obviousness. The Examiner is pointed to MPEP 716.02, which discusses unexpected results.

As disclosed throughout the specification, for example at page 8, and in the example section, the treatment protocol of

the instant invention produces increased treatment efficacy. This is because patients treated using a chronic intermittent treatment schedule are less likely to become tolerant to the medications.

Therefore, in light of the clear differences in treatment protocols, and the above mentioned unexpected results, claims 1-18 are patentable over US Patents 5,792,995 and 6,329,422 to Fischer et al. Accordingly, Applicants respectfully request that the rejection of claims 1-18 under 35 U.S.C. §103 be withdrawn.

CONCLUSION

In view of the amendments and remarks presented herein, it is respectfully urged that the rejections set forth in the March 12, 2003 Official Action be withdrawn and that this application be passed to issue. In the event the Examiner is not persuaded as to the allowability of any claim, and it appears that any outstanding issues may be resolved through a telephone interview, the Examiner is requested to telephone the undersigned attorney at the phone number given below.

Respectfully submitted,

DANN, DORFMAN, HERRELL AND SKILLMAN
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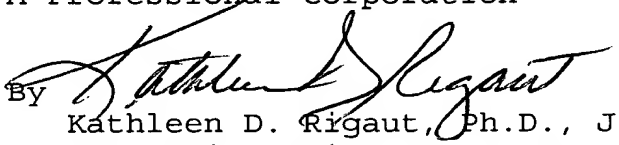
By 
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